REVIEW

Endocrine and Metabolic Manifestations of Invasive Fungal Infections and Systemic Antifungal Treatment

MICHAIL S. LIONAKIS, MD, SCD; GEORGE SAMONIS, MD; AND DIMITRIOS P. KONTOYIANNIS, MD, MS, SCD

Systemic fungal infections are increasingly reported in immunocompromised patients with hematological malignancies, recipients of bone marrow and solid organ allografts, and patients with AIDS. Mycoses may infiltrate endocrine organs and adversely affect their function or produce metabolic complications, such as hypopituitarism, hyperthyroidism or hypothyroidism, pancreatitis, hypoadrenalism, hypogonadism, hypernatremia or hyponatremia, and hypercalcemia. Antifungal agents used for prophylaxis and/or treatment of mycoses also have adverse endocrine and metabolic effects, including hypoadrenalism, hypogonadism, hypoglycemia, dyslipidemia, hypernatremia, hypocalcemia, hyperphosphatemia, hyperkalemia or hypokalemia, and hypomagnesemia. Herein, we review how mycoses and conventional systemic antifungal treatment can affect the endocrine system and cause metabolic abnormalities. If clinicians are equipped with better knowledge of the endocrine and metabolic complications of fungal infections and antifungal therapy, they can more readily recognize them and favorably affect outcome.

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ADH = antidiuretic hormone; AMB = amphotericin B; CYP = cytochrome P; DI = diabetes insipidus; LDL-C = low-density lipoprotein cholesterol; LH = luteinizing hormone; SIADH = syndrome of inappropriate ADH production

The incidence of systemic fungal infections is increasing in immunocompromised patients. Because these infections frequently disseminate, they may affect the function of the pituitary, thyroid, parathyroid, and adrenal glands; the pancreas; and the reproductive organs. Metabolic complications, such as electrolytic abnormalities, can also occur. Agents used for prophylaxis and/or treatment of mycoses also have adverse endocrine and metabolic effects (Table 1). We review how mycoses affect the endocrine system and cause metabolic derangements and discuss the endocrine and metabolic complications of antifungal agents. The focus is on only systemic antifungal agents for invasive mycoses, such as the polyenes (mainly amphotericin B [AMB] and its lipid formulations), the azoles (fluconazole, itraconazole, voriconazole, posaconazole, and ketoconazole), and the echinocandins (caspofungin, micafungin, and anidulafungin). Agents that are used topically or have antifungal properties, such as pentamidine, trimethoprim-sulfamethoxazole, dapsone, and atovaquone, are not discussed.

We searched the MEDLINE and PubMed databases (from 1966 to February 2008) and abstracts from major infectious disease meetings held from 1992 to 2007 for published reports pertaining to the endocrine and metabolic manifestations of invasive mycoses and their antifungal treatment using terms such as *endocrine*, *metabolic*, *electrolytes*, *fungal*, *molds*, *yeast*, *aspergillosis*, *candida*, *pituitary*, *thyroid*, *pancreas*, *adrenal*, *ovaries*, *reproductive system*, *sodium*, *potassium*, *calcium*, *phosphorous*, *dyslipidemia*, *amphotericin B*, *azoles*, and *echinocandins*. Studies were selected on the basis of the importance of data (as determined by frequency of citations by subsequent publications in the specialty) and originality. Review articles by thought leaders in mycology and endocrinology were also included in our search.

PITUITARY INVOLVEMENT AND DYSFUNCTION

MYCOSES

In pituitary infections, which are rare, bacteria are the most common infecting microbes, whereas fungi are much less frequent.[1] Interestingly, the pituitary gland has a role in innate antifungal immunity; Breuel et al[2] showed that pituitary receptors sense circulating *Candida* glucans and respond by Toll-like receptor 4 (*TLR4*) and *CD14* gene expression.

Pituitary involvement is also rare in patients with central nervous system fungal infections. Of 40 patients with intracranial fungal infections, only 6 (15%) had sellar distribution.[3] Various mycoses can infiltrate the pituitary gland[1,3-11] (Table 2). The pathogenesis of pituitary fungal infection involves (1) hematogenous spread, typically seen with disseminated opportunistic yeast or mold infections in immunosuppressed hosts; (2) extension from adjacent anatomical sites (ie, cryptococcal meningeal infection or aspergillosis of the sphenoid sinus, cavernous sinus, and skull base); or (3) iatrogenic inoculation (eg, with *Aspergillus* or *Candida* species) during transsphenoidal adenoma resection.[1,3,4]

Pituitary fungal infections have no specific clinical features; like any pituitary process, they may cause headache, ophthalmoplegia due to optic chiasm compression, and/or

From the Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas M. D. Anderson Cancer Center, Houston (M.S.L., D.P.K.); and University Hospital of Heraklion, University of Crete, Heraklion, Greece (G.S.)

Individual reprints of this article are not available. Address correspondence to Dimitrios P. Kontoyiannis, MD, MS, ScD, Department of Infectious Diseases, Infection Control and Employee Health, Unit 402, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030 (dkontoyi@mdanderson.org).

TABLE 1. **Adverse Endocrine and Metabolic Effects of Systemic Antifungal Agents**

Antifungal agent	Endocrine effects	Metabolic effects
Polyenes		
Amphotericin B	Oligospermia in animals	Hypernatremia, hypokalemia, hyperkalemia, hypomagnesemia, hypocalcemia
Lipid formulations of amphotericin B	Pancreatitis	Hypernatremia, hypokalemia, hyperkalemia, hypomagnesemia, hypocalcemia, hyperphosphatemia, pseudohyperphosphatemia
Nystatin	Oligospermia in animals	Hypokalemia, hypomagnesemia, hypocalcemia
Azoles		
Ketoconazole	Hypothyroidism, Addison disease, decreased libido, impotence, gynecomastia, menstrual irregularities	Hypokalemia, hypocalcemia, hypoglycemia, dyslipidemia
Fluconazole	Pancreatitis, Addison disease, Conn-like syndrome, menstrual irregularities	Hypokalemia, hypoglycemia
Itraconazole	Pancreatitis, Addison disease, Conn-like syndrome, decreased libido, impotence, gynecomastia, menstrual irregularities	Hypokalemia, dyslipidemia
Voriconazole	Pancreatitis	Hypokalemia, hypomagnesemia, hypoglycemia, dyslipidemia
Posaconazole	Menstrual irregularities	None reported
Echinocandins		
Caspofungin, anidulafungin, micafungin	Pancreatitis	Hypokalemia, hypomagnesemia, hypercalcemia
Other systemic antimicrobial agents with antifungal properties		
Griseofulvin	Pancreatitis	None reported
Potassium iodide	Thyrotoxicosis (Jod-Basedow disease), hypothyroidism (Wolff-Chaikoff effect)	Hyperkalemia

endocrine dysfunction.[1,3,4,11] Most such infections have no overt endocrine symptoms. However, hypopituitarism occurs rarely, manifesting most often as decreased libido and menstrual abnormalities because of luteinizing hormone (LH) and follicle-stimulating hormone insufficiency.[11,12] Moreover, diabetes insipidus (DI) presenting as polydipsia and polyuria from impaired antidiuretic hormone (ADH) release is not uncommon.[1,3,4,11,12] Indeed, DI occurs more frequently with pituitary infections than with adenomas, implying that posterior pituitary function is affected early during pituitary infections.[1,12] Hyperprolactinemia and decreases in thyrotropin-releasing hormone and corticotropin also occur; conversely, endocrine function may be normal.[1,3,4,11,12]

Fungal pituitary infections are radiographically indistinguishable from intrasellar bacterial infections and tumors. Consequently, they are often misdiagnosed as tumors, and diagnosis is made unexpectedly after surgery or at autopsy.[1,4-11] Certain magnetic resonance imaging findings are thought to be specific for pituitary infection. Therefore, when peripheral enhancement, hypointensity, or calcifications are seen on T2-weighted images, infection is favored over a tumor.[7] Investigators have used gallium-67 imaging for postoperative follow-up of patients with pituitary abscesses caused by *Aspergillus* spp, but more studies are needed to establish the role of imaging modalities in these patients.[13] The mortality rate with pituitary fungal infections exceeds 70% because of delayed recognition and the typically disseminated nature of these infections.[1,10] Treatment comprises antifungal therapy and transsphenoidal resection, which is preferred over craniotomy to prevent intracranial dissemination.[1]

Fungal infections can also influence sodium homeostasis by affecting pituitary ADH release. Hypernatremia secondary to DI or hyponatremia caused by the syndrome of inappropriate ADH production (SIADH) can develop in patients with mycoses. Diabetes insipidus occurs primarily with cryptococcal basilar meningitis[14] but also with aspergillosis, candidiasis, zygomycosis, and blastomycosis.[1,4,6,11,15,16] Fungal cryptococcal and coccidioidal meningitis rarely cause SIADH[17,18]; the incidence of SIADH in patients with cryptococcal meningitis is approximately 8%.[17] A well-recognized cause of SIADH is pneumonia.[12] Any fungal pneumonia can be complicated by SIADH. *Pneumocystis* pneumonia, caused by *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*), is reportedly the most common cause of SIADH in patients with AIDS; antifungal treatment often corrects hyponatremia.[19]

Antifungal Agents

Antidiuretic hormone acts by aquaporin 2–induced increase of the water permeability of renal collecting tubules.

TABLE 2. **Mycoses Reported to Infiltrate Various Organs of the Endocrine System**[a]

Fungal infection	Pituitary gland	Thyroid gland	Pancreas	Adrenal gland	Male reproductive organs	Female reproductive organs
Aspergillosis	+	35.0%	4.7%	5.0%	+	+
Zygomycosis	–	3.0%	+	–	–	–
Fusariosis	–	–	+	–	+	–
Scedosporiosis	–	+	+	+	+	–
Scopulariopsis infection	+	+	–	–	–	–
Candidiasis	+	8.0%	2.9%	5.0%	–	+
Cryptococcosis	+	12.0%	3.8%	15.0%	+	+
Histoplasmosis	–	+	+	82.0%	+	+
Blastomycosis	–	+	+	10.0%	10.0%	+
Coccidioidomycosis	+	6.0%	+	36.0%	+	+
Paracoccidioidomycosis	+	4.0%	+	80.0%	+	+
Sporotrichosis	–	–	+	+	+	–
Trichosporonosis	–	+	+	–	–	+
Pneumocystosis	+	23.0%[b]	9.0%	15.0%[b]	–	–
Basidiobolomycosis	–	–	+	+	–	+
Chromoblastomycosis	–	–	+	–	–	–
Saccharomyces spp infection	–	–	+	–	–	–
Malassezia spp infection	–	–	+	+	–	–
Trichophyton spp infection	–	–	–	–	+	–

[a] The percentages for postmortem infiltration of different endocrine organs correspond to the highest reported rate of infiltration in the literature. In cases in which infiltration is sporadic, percentages are not provided. + = sporadic infiltration; – = not reported in the literature.
[b] Percentages refer to cases of extrapulmonary pneumocystosis.

Amphotericin B decreases aquaporin 2 expression in the kidney medulla, makes collecting tubules insensitive to ADH, and may rarely cause reversible nephrogenic DI.[20,21] It also causes hypokalemia, a well-known etiology of nephrogenic DI; however, nephrogenic DI can occur without hypokalemia.[20,21] Higher levels of prostaglandin E_2 and increased apoptosis seem to contribute to AMB-mediated DI.[22,23] Amelioration of DI can be achieved with amiloride plus hydrochlorothiazide, indomethacin, and replacement of AMB-deoxycholate by lipid AMB formulations, which (for reasons that are not understood) cause DI less often.[21,22,24]

THYROID INVOLVEMENT AND DYSFUNCTION

Mycoses

The thyroid is resistant to microbial invasion because of its rich blood supply, iodine content, and capsule.[25] Although several fungi may infect the thyroid[25-44] (Table 2), thyroid fungal infection occurs rarely and is clinically overt in a minority of patients.[25-27] Of 415 previously reported cases of infectious thyroiditis (1900-1997), only 50 (12%) were fungal.[25-27] The pathogenesis of fungal thyroiditis entails hematogenous or lymphatic spread.[25] Although most cases of thyroid fungal involvement occur during dissemination in immunosuppressed patients, isolated thyroid histoplasmosis, coccidioidomycosis, and pneumocystosis have been reported.[38,40,44]

Aspergillus spp are the predominant causative fungus for thyroiditis and asymptomatic thyroid infiltration.[25-31] The literature contains 21 case reports of overt thyroiditis caused by *Aspergillus* spp, with thyroid infiltration found postmortem in 10% to 35% of aspergillosis cases.[25-31] In contrast, thyroid infiltration is less common in other mycoses[9,25-32,36,45-49] (Table 2). Unsurprisingly, *P jiroveci* is the most common cause of fungal thyroiditis in patients with AIDS, reflecting the high incidence of pneumocystosis in these patients.[12,44] Thyroiditis caused by *P jiroveci* is typically associated with aerosolized pentamidine prophylaxis, a known risk factor for extrapulmonary pneumocystosis.[44] In most cases, thyroid fungal involvement is an incidental finding at autopsy without antemortem evidence of thyroid dysfunction.[12,25] Nevertheless, it can manifest as subacute thyroiditis with local and systemic symptoms.[25] Neck swelling and tenderness are common because of thyroid enlargement and dysphagia from esophageal compression; in severe cases, fatal respiratory failure from tracheal obstruction has occurred.[25,28,50] Fungal thyroiditis typically begins with a brief hyperthyroid phase in which glandular destruction causes thyroid hormone release.[12,25] Transient euthyroidism ensues, followed by hypothyroidism and, ultimately, recovery to euthyroidism.[12,25] Hence, symptoms and laboratory evidence can range from those characteristic of hyperthyroidism (or even frank thyrotoxicosis) to those typical of hypothyroidism from fungal involvement, depending on the phase in which the condition is diagnosed.[12,25] Hyperthyroidism is more common with aspergillosis and coccidioidal infection, whereas hypothyroidism is more common with thyroiditis caused by *P jiroveci*.[12,25-29,37,44] Whether this

pattern reflects the degree of glandular dysregulation by the aforementioned fungi or results from differences in the timing of diagnosis remains unknown.

Patients with acute severe fungal infections may develop euthyroid sick syndrome, characterized by decreased levels of triiodothyronine and increased levels of normal thyroxine and thyrotropin-releasing hormone, as described in cases of paracoccidioidomycosis.[51] Because such laboratory findings signify diminished peripheral conversion of thyroxine to triiodothyronine, thyroid replacement therapy is unnecessary and detrimental.[52] However, in one study, a decreased total triiodothyronine level was the best prognostic indicator of death from pneumonia caused by *P jiroveci* in patients with AIDS.[53]

Besides direct fungal invasion of the thyroid, mycotoxin secretion may influence thyroid function.[54,55] Specifically, at doses relevant to human exposure levels, the *Aspergillus* toxin patulin decreased thyroxine levels in animals, and the *Fusarium* toxin deoxynivalenol increased them.[54,55] Whether mycotoxin secretion during fungal infections affects thyroid function in humans remains unstudied.

Antifungal Agents

In preclinical studies, imidazoles, such as ketoconazole, have had antithyroid effects because of interference with iodine and thyroid peroxidase.[56] Nevertheless, administration of 200 to 600 mg/d of ketoconazole for 1 month did not affect thyroid function in euthyroid, hyperthyroid, or hypothyroid patients.[57,58] However, high-dose ketoconazole (1200 mg/d) may cause hypothyroidism.[59] Hypothyroidism also developed in 2 patients with chronic mucocutaneous candidiasis after prolonged (>3 months) low-dose (100-200 mg/d) treatment with ketoconazole.[60] Because patients with chronic mucocutaneous candidiasis frequently have hypothyroidism associated with adult polyglandular autoimmune syndrome type I, it remains unclear whether ketoconazole induced hypothyroidism in these patients.[60] No studies have implicated the triazoles in thyroid dysfunction.[61]

Use of potassium iodide is common in treating cutaneous sporotrichosis.[62] Prolonged (>1 month) potassium iodide treatment is associated with reversible thyrotoxicosis in patients with coexistent "hot" thyroid nodules (Jod-Basedow disease) and with hypothyroidism in patients with excessive autoregulation (Wolff-Chaikoff effect).[62]

CALCIUM AND PHOSPHORUS ABNORMALITIES AND PARATHYROID INVOLVEMENT

Mycoses

Hypercalcemia is a well-known complication of many granulomatous disorders, including sarcoidosis, tuberculosis, and lymphomas.[63] It is derived from extrarenal dysregulated production of 1,25-dihydroxyvitamin D due to interferon-γ–mediated expression of 1α-hydroxylase by activated macrophages in granulomas.[64] Chronic fungal infections, including histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, candidiasis, cryptococcosis, and pneumocystosis, can also cause granulomas and reversible hypercalcemia.[65-70] Reports indicate that 3% of patients with various mycoses have hypercalcemia, whereas about 10% of patients with sarcoidosis do.[65-70] Whether this reflects variation in granuloma formation or subtle differences in the mechanisms of hypercalcemia between these entities is unclear.

Studies have shown that the mechanisms of hypercalcemia differ with the various mycoses. For instance, coccidioidomycosis, the mycosis most commonly associated with hypercalcemia (incidence, 1.4%-25.0%), typically manifests late after initiation of antifungal treatment.[67,68] Parathyroid hormone and parathyroid hormone–related peptide levels are normal. Hypercalcemia in coccidioidomycosis is not triggered by autonomous 1,25-dihydroxyvitamin D, prostaglandin, or osteoclast-activating factor production.[67,68] Osseous coccidioidomycosis that causes bone resorption contributes in some cases, but hypercalcemia occurs even without bone involvement. Thus, the presence of an osteotropic substance resembling humoral hypercalcemia of malignancy has been postulated.[67,68] Elevated levels of nephrogenous cyclic adenosine monophosphate, low levels of 1,25-dihydroxyvitamin D, and hypercalciuria with coccidioidomycosis have also been described in patients with hypercalcemia of malignancy.[71]

In contrast, studies have shown autonomous 1,25-dihydroxyvitamin D production with candidiasis, cryptococcosis, paracoccidioidomycosis, pneumocystosis, and histoplasmosis.[65-67,69,70] Hypercalcemia has also been reported as part of the immune reconstitution syndrome in patients with AIDS and cryptococcosis after initiation of antiretroviral therapy.[72] The underlying mechanism remains unclear, but it has been postulated that hypercalcemia is caused by restoration of the granulomatous host response, resulting in autonomous 1,25-dihydroxyvitamin D production after antiretroviral therapy.[73]

Osteopontin, a glycoprotein ligand of the $\alpha_v\beta_3$ integrin that activates macrophages and osteoclasts,[74] is highly expressed by histiocytes in granulomas of diverse etiologies, including histoplasmosis.[75] Osteoclasts synthesize osteopontin and $\alpha_v\beta_3$ integrin, which both localize at bone resorption sites.[74] Hence, osteopontin may contribute to hypercalcemia via osteoclast activation and bone resorption; further studies are needed to elucidate its role in hypercalcemia associated with fungal infections. Another molecule implicated in osteoclast activation and bone resorption in

hypercalcemia of malignancy is the receptor activator of nuclear factor-κβ ligand; its role in hypercalcemia of mycoses also merits investigation.[76]

Conversely, hypocalcemia and hyperphosphatemia caused by hypoparathyroidism have been described in a patient with pneumocystosis and parathyroid infiltration.[77] Supplementation with vitamin D and calcium was necessary to maintain eucalcemia.

Antifungal agents

Azoles inhibit ergosterol biosynthesis by blocking cytochrome P (CYP) 450–dependent 14α-lanosterol demethylase.[78] The reported higher frequency of endocrine complications of ketoconazole than of other azoles derives from their different selectivity for fungal vs mammalian CYP450-dependent 14α-lanosterol demethylase.[78]

Ketoconazole inhibits in vitro conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by competitive inhibition of CYP450-dependent 1α-hydroxylase.[79] Administration of 600 to 900 mg/d of ketoconazole has been shown to cause a rapid, dose-dependent decrease of 40% to 45% in 1,25-dihydroxyvitamin D levels in healthy participants and in patients with hyperparathyroidism, sarcoidosis, and tuberculosis, resulting in calcium-lowering in some, but not all, patients.[80-82] Conversely, the triazoles do not affect calcium homeostasis.

Polyene-induced hypomagnesemia resulting from iatrogenic Fanconi syndrome can cause hypocalcemia by adversely affecting parathyroid hormone secretion and action in the kidney.[83,84] Cases of AMB- and nystatin-induced hypoparathyroidism and hypocalcemia have been reported.[83,84] Conversely, caspofungin has been reported to induce hypercalcemia, but the mechanism by which it does so remains unknown.[85]

Phosphate abnormalities are rarely associated with antifungal use. Specifically, because each 50-mg vial of liposomal AMB contains 37 mg of phosphorus, prolonged treatment with high-dose liposomal AMB can result in hyperphosphatemia, especially in patients with impaired renal function.[86] Nevertheless, because liposomal AMB can interfere with the Synchron LX-20 phosphorus assay (Beckman Coulter, Fullerton, CA), pseudohyperphosphatemia can occur, and caution is required before institution of phosphate-lowering therapy.[87]

PANCREATIC INVOLVEMENT AND DYSFUNCTION

Mycoses

Fungi may involve the pancreas in 2 patterns. The first is hematogenous involvement during dissemination[9,34,45-49,88-98] (Table 2). Unless more than 80% of pancreatic tissue is affected, pancreatic insufficiency does not develop; thus, involvement is asymptomatic and usually discovered postmortem. The second pattern is seeding by *Candida* spp of pancreatic tissue or pseudocysts after necrotizing pancreatitis.[99,100] The incidence of such infection has increased considerably from about 7% of total postpancreatic infections in the 1980s to 40% in the 2000s after routine administration of prophylactic antibiotics in patients with necrotizing pancreatitis.[99,100] Besides antibiotic prophylaxis that predisposes patients to fungal superinfection, the risk factors for fungal pancreatic infection are postpancreatitis abdominal surgical manipulation and the global immune dysregulation seen with necrotizing pancreatitis, as evidenced by decreases in CD4 lymphocytes and interleukin 2.[99-101]

Most infections occur within 1 month after pancreatitis and derive from *Candida* spp translocated from the gut.[99,100] Aspartic proteinase 6, secreted by *Candida* spp and regulated by the enhanced filamentous growth 1 (*EFG1*) transcription factor, has a role in enabling *Candida* spp to invade pancreatic tissue.[102] In most studies, pancreatic candidal infection is associated with higher mortality rates than is bacterial pancreatic infection.[99] However, not all studies have shown such an association.[99] Interventions proposed to prevent pancreatic seeding by fungi in high-risk patients with necrotizing pancreatitis are selective bowel decontamination and fluconazole prophylaxis.[99,100] The former approach is controversial; the latter decreases the incidence of such infections, but this reduction does not translate into survival benefits and carries the risk of selecting azole-resistant *Candida* spp.[99,100]

Antifungal Agents

Pancreatitis is rarely reported after treatment with griseofulvin, liposomal AMB (0.5%-1% of patients), micafungin, fluconazole, itraconazole, and voriconazole.[103-107] Elevated levels of serum voriconazole can cause hypoglycemia, although the underlying mechanism is not understood and merits investigation.[107] Asian patients, who frequently have the CYP2C19 sequence variation that causes increased drug concentrations, may be especially predisposed to voriconazole-induced hypoglycemia.[108] Ketoconazole and fluconazole have also been associated with development of hypoglycemia.[109,110] The mechanism for the former is unknown, whereas coadministration of fluconazole with oral hypoglycemic agents to patients with diabetes may inhibit the metabolism of the latter compounds and elevate their levels, thus predisposing patients to hypoglycemia.[109,110] This interaction appears dose-dependent and agent-specific. Therefore, coadministration of 100 mg/d of fluconazole with tolbutamide or 200 mg/d of fluconazole with glimepiride or nateglinide increased the peak plasma concentrations and the area under the curve

of these compounds, hence heightening the risk of hypoglycemia.[111,112] In contrast, coadministration of 50 mg/d of fluconazole with gliclazide or glibenclamide did not affect glycemic homeostasis.[113] People with CYP2C9 sequence variations have a markedly diminished capacity to metabolize CYP2C9 substrates and might be particularly at risk for hypoglycemia in the setting of azole-hypoglycemic drug coadministration.[114] However, more studies are needed to elucidate the frequency and relative risk of hypoglycemia as a result of different azole–hypoglycemic agent interactions.

ADRENAL INVOLVEMENT AND DYSFUNCTION

Mycoses

The adrenal glands are the most common endocrine organs involved during infections, including mycoses. Frenkel[115] suggested that excessive glucocorticoid levels in adrenal circulation (ie, 20-40 times higher than in the peripheral blood) generate local cell-mediated immunosuppression that predisposes patients to glandular invasion by microorganisms.

Isolated adrenal involvement has been reported in immunocompetent hosts with histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, and pneumocystosis.[116-119] Much more often, the adrenal glands are involved in widely disseminated mycoses; at autopsy, histoplasmosis and paracoccidioidomycosis are by far the most common fungal infections found to have infiltrated the adrenal glands[9,34,45-49,92-95,98,120-123] (Table 2). Most such cases are asymptomatic, and antemortem diagnosis is rare. Adrenal function remains unaffected unless more than 90% of the adrenal cortex is obliterated, and so patients with disseminated mycoses may die of their infection before such destruction occurs.[120-123] Also, manifestations of adrenal insufficiency are nonspecific and may be attributed erroneously to the mycosis.[120-123]

In addition to directly destroying adrenal tissue, host humoral factors generated during systemic infections, such as corticostatins/defensins, may contribute to adrenal dysfunction. Specifically, these molecules inhibit adrenal steroidogenesis by interfering with corticotropin affinity at the receptor level; their role in affecting adrenal steroidogenesis in patients with systemic mycoses should be further explored.[124]

Addison disease has been reported with histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, cryptococcosis, blastomycosis, pneumocystosis, candidiasis, and infection with *Bipolaris* spp.[118,120,122,123,125,126] Of these infections, histoplasmosis and paracoccidioidomycosis have the highest proclivity for the adrenal glands, and Addison disease occurs most frequently in patients with these infections (histoplasmosis, 7%-12%; paracoccidioidomycosis, 9%-14%).[9,93,121] Prompt recognition and glucocorticoid supplementation are fundamental for survival in such patients. In patients with blastomycosis and histoplasmosis, latency periods of several years between primary infection and adrenal insufficiency are not uncommon, signifying reactivation of quiescent adrenal foci.[93,116,123]

Most adrenal insufficiency cases are irreversible and necessitate lifelong glucocorticoid supplementation. Nevertheless, recovery of adrenal function has been reported with antifungal treatment in histoplasmosis and paracoccidioidomycosis cases.[127,128] Autopsy studies of paracoccidioidomycosis revealed fungal vasculitis in small arterioles, leading to tissue ischemia early during adrenal invasion.[119] If left untreated, progression to glandular necrosis and irreversible endocrine impairment occur.[119] Hence, prompt antifungal therapy may prevent irreversible pathological changes and salvage adrenal function.

Adrenal reserve can also be affected by systemic mycoses, such as histoplasmosis, cryptococcosis, coccidioidomycosis, paracoccidioidomycosis, pneumocystosis, and blastomycosis.[93,116-118,120,123] In particular, 50% of patients with paracoccidioidomycosis have diminished adrenal reserve, as evidenced by attenuated cortisol increments after corticotropin administration.[129] Such patients are asymptomatic, but fatal adrenal failure can occur in conditions of physiological stress. Hence, when the condition of patients with mycoses unexpectedly deteriorates, the adrenal axis should be examined thoroughly.

Fungi might have differing affinities for infiltration of the different adrenal zones. For example, *Paracoccidioides* spp commonly infiltrate the zona reticularis, lowering dehydroepiandrosterone sulfate levels.[129,130] Such a shift in adrenal steroidogenesis away from androgens and toward the essential glucocorticoid pathway is presumably an adaptive mechanism with infections.[130] Such patients may have impaired mineralocorticoid secretion with decreased aldosterone levels and elevated plasma renin activity because of zona glomerulosa infiltration. Mineralocorticoid deficiency can cause hyponatremia, hyperkalemia, and metabolic acidosis.[120-123] In contrast, in patients with histoplasmosis, sparing of the zona glomerulosa and preservation of mineralocorticoid function is the rule.[93]

Fungal adrenal involvement manifests radiographically as glandular enlargement with peripheral enhancement, central hypoattenuation, contour preservation, and calcifications during healing.[131] Histoplasmosis causes bilateral symmetric adrenal enlargement, whereas paracoccidioidomycosis and blastomycosis cause asymmetric and occasionally unilateral involvement.[131] These characteristics help differentiate fungal adrenal infections from metastatic disease, in which the adrenal contour is distorted, and from autoimmune adrenalitis, in which the glands are atrophic.[131]

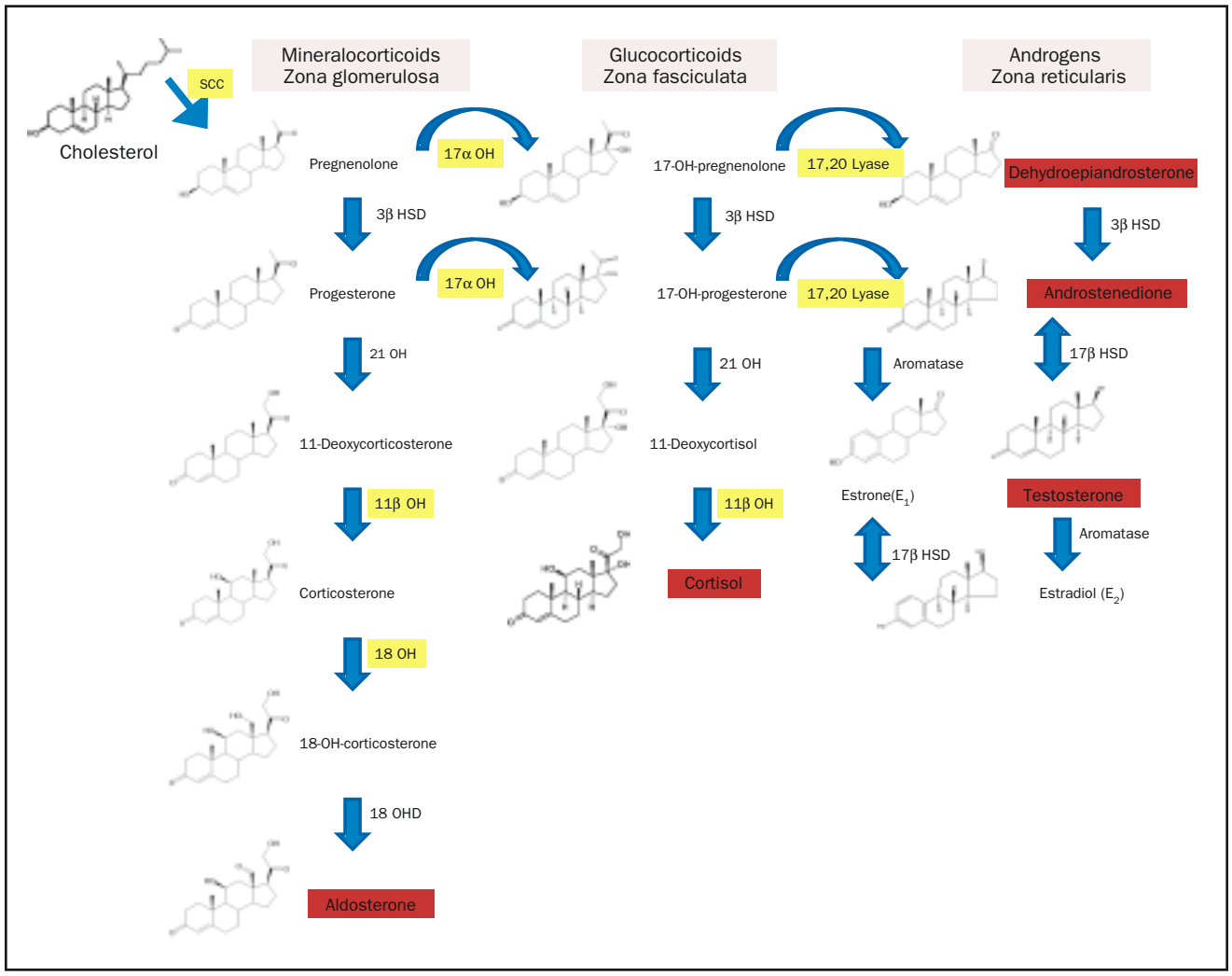

FIGURE. The main pathways of steroidogenesis in the adrenal glands and inhibitory effects of ketoconazole. The principal enzymes inhibited by ketoconazole are shown in yellow, and the main steroid products whose synthesis is decreased by ketoconazole are shown in red. H = hydrogen; HSD = hydroxysteroid dehydrogenase; O = oxygen; OH = hydroxylase; OHD = hydroxy dehydrogenase; SCC = cholesterol side-chain cleavage.
Adapted from Hardman JG, Limbird LE, Gilman AG. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 11th ed. New York, NY: McGraw-Hill, 2006, with permission of McGraw-Hill.

Antifungal Agents

Azoles affect glucocorticoid and mineralocorticoid function by inhibiting CYP450-dependent enzymes involved in adrenal steroidogenesis. Specifically, ketoconazole is a dose-dependent reversible inhibitor of cholesterol desmolase, 17,20-lyase, 11β-hydroxylase, 17α-hydroxylase, and 18-hydroxylase (Figure).[132-134] Critical factors that modulate ketoconazole's endocrine effects are dosage and timing of administration because the kinetics of adrenal inhibition reflect serum ketoconazole concentrations.[132-135] Thus, no effect on glucocorticoid synthesis is seen after administration of 200 mg of ketoconazole.[135,136] However, use of 400 or 600 mg of ketoconazole transiently blunts plasma cortisol response to corticotropin without affecting basal cortisol or pituitary corticotropin secretion.[134-137] This effect lasts 8 hours but normalizes by 16 hours after ketoconazole administration.[134-137] Higher doses produce more pronounced adrenal dysfunction. Nevertheless, overt adrenal insufficiency is relatively infrequent with ketoconazole, presumably because of a compensatory increase in corticotropin. However, overt adrenal insufficiency can occur with administration of 600 to 1200 mg/d of ketoconazole in divided doses; as opposed to once-daily ketoconazole use, such regimens produce sustained adrenal inhibition with-

out allowing for compensatory normalization of adrenal steroidogenesis for a substantial part of the day.[134-138] In contrast, adrenal crisis has occurred with ketoconazole dosages as low as 400 mg/d, suggesting host-specific genetic susceptibility to adrenal dysfunction.[139]

In addition to inhibiting glucocorticoid synthesis, ketoconazole is a dose-dependent, reversible, competitive antagonist at the glucocorticoid receptor level.[140] In fact, because of its antiglucocorticoid properties and rapid action onset, physicians have used ketoconazole (800-1200 mg/d) in palliative treatment of Cushing disease, adrenal tumors, and ectopic corticotropin production by small-cell lung carcinoma or carcinoid tumors.[141-143] The aforementioned interaction of ketoconazole with the glucocorticoid receptor is restricted to imidazoles and does not occur with triazoles.[144]

Clinicians have used ketoconazole's ability to inhibit mineralocorticoid synthesis for palliative treatment of primary hyperaldosteronism due to adrenal adenomas or hyperplasia.[135,145] However, the accumulation of 11-deoxycortisol, corticosterone, and 11-deoxycorticosterone induced by inhibition of cortisol and aldosterone synthesis (Figure) can cause hypersensitivity to the mineralocorticoid properties of these compounds; indeed, hypertension develops in 14% to 27% of patients after long-term high-dose ketoconazole use; hypokalemia and edema may also develop, suggesting ketoconazole-induced Conn syndrome.[146]

Fluconazole inhibits CYP450-dependent enzymes in cell cultures and animals, but concentrations required for these effects far exceed its therapeutic range. Consequently, adrenal function is unaffected in patients receiving 400 mg/d of fluconazole.[147,148] However, the literature contains several reports of fluconazole-induced reversible Addison disease occurring within 24 to 48 hours of treatment.[147,149] Critically ill patients already at increased risk of adrenal insufficiency who receive high-dose fluconazole (800 mg/d) are most predisposed to developing adrenal insufficiency; however, it has been reported even with dosing of 200 mg/d.[149] Fluconazole has reversed hypercortisolism in adrenal carcinoma–induced Cushing syndrome cases.[150]

Although itraconazole does not inhibit adrenal steroidogenesis at 100 to 400 mg/d,[151] reversible adrenal insufficiency has been reported at 600 mg/d.[152] Also, combination of itraconazole with high-potency inhaled glucocorticoids can suppress the hypothalamic-pituitary-adrenal axis.[153] Such suppression occurs because itraconazole, an inhibitor of CYP3A4, decreases glucocorticoid clearance and increases serum glucocorticoid levels.[154] In a study of 25 patients receiving itraconazole and inhaled budesonide, adrenal insufficiency developed in 11 patients and Cushing syndrome in 1 patient.[153] Adrenal function recovered in only 1 patient, whereas the remaining 10 had persistent adrenal insufficiency 2 to 10 months after treatment discontinuation.[153] Variation in CYP3A4 activity or glucocorticoid receptor sequence variations may explain such host-specific phenotypic diversity in adrenal function manifestations.[155] In addition, mineralocorticoid-induced edema, hypokalemia, and hypertension have been reported in 63% of patients receiving high-dose itraconazole (600 mg/d).[152] No adrenal effects have been reported with voriconazole or posaconazole.

POTASSIUM AND MAGNESIUM ABNORMALITIES INDUCED BY ANTIFUNGAL AGENTS

Hypokalemia develops in up to 90% of AMB-deoxycholate–treated patients and may occur and persist even weeks after treatment discontinuation.[156] Amphotericin B forms intramembranous pores in distal convoluted renal tubules, increasing their permeability and potassium urinary wasting.[156] Apoptosis is an important modulator of this process.[23] Additionally, AMB causes renal tubular acidosis type I because of a defect in distal tubule hydrogen potassium adenosine triphosphatase and promotes potassium urinary loss.[156] Moreover, AMB enhances sodium reabsorption in the distal colon, causing fecal potassium loss.[156] A recent study suggested that preexisting proteinuria may protect from AMB-deoxycholate–induced hypokalemia because binding of AMB to albumin in the tubular lumen may decrease the free drug fraction available to bind to the luminal epithelial surface.[157]

Reversible, dose-dependent hypokalemia is more often caused by AMB-deoxycholate than by lipid AMB formulations[156]; the latter have less affinity for mammalian cell membranes, thus reducing the incidence of nephrotoxicity. However, dose-dependent liposomal AMB–induced hypokalemia does occur; a recent study showed a 30% and 16% incidence of hypokalemia (potassium level <3 mEq/L [to convert to mmol/L, multiply by 1.0]) in patients treated with 10 vs 3 mg/kg of liposomal AMB daily, respectively.[158] Hypokalemia can be ameliorated by administration of amiloride or spironolactone or by dilution of AMB in fat emulsion instead of dextrose.[159-161] Nystatin causes hypokalemia by a similar mechanism.[84] Fluconazole, itraconazole, and voriconazole also cause hypokalemia in up to 9%, 12%, and 16% of treated patients, respectively.[162,163] Ventricular fibrillation and rhabdomyolysis have been reported with severe itraconazole-mediated hypokalemia.[164] Echinocandins cause hypokalemia in 2% to 11% of patients, and studies have suggested a dose-dependent hypokalemic effect for caspofungin.[85,165] The precise mechanisms by which azoles and echinocandins cause hypokalemia have not been elucidated.

The AMB lipid complex and AMB-deoxycholate are also associated with hyperkalemia via intracellular potassium

shift.[166] Renal insufficiency and rapid infusion (<1 hour) increase AMB serum levels and the risk of hyperkalemia and ventricular fibrillation[166]; this increased risk can be avoided by slower infusion (4-6 hours) and AMB administration during hemodialysis.[166] Renal failure also predisposes potassium iodide–treated patients to hyperkalemia.[62]

Hypomagnesemia occurs in 30% to 75% of AMB-treated patients because of increased urinary magnesium secretion from AMB-induced tubular defects in distal convoluted tubules.[83,167] The incidence of hypomagnesemia increases during the second week of AMB administration, peaks by the fourth week, and then plateaus.[167] Hypomagnesemia, which is dose-dependent and reversible, is more common with AMB-deoxycholate than with lipid AMB formulations; it may persist for weeks after AMB discontinuation.[167] Amiloride ameliorated AMB-mediated hypomagnesemia in some studies.[159] Up to 63% of patients treated with voriconazole and up to 3% of those treated with caspofungin have been shown to develop hypomagnesemia.[85,163,165]

EFFECTS OF ANTIFUNGAL AGENTS ON LIPID METABOLISM

Ketoconazole inhibits cholesterol synthesis in a dose-dependent fashion by blocking conversion of lanosterol to cholesterol.[78,168] Other lipid-modifying properties of ketoconazole include inhibition of macrophage-induced low-density lipoprotein cholesterol (LDL-C) oxidation, decreased lipoprotein lipase and 3-hydroxy-3-methylglutaryl coenzyme A reductase activities, inhibition of intestinal cholesterol absorption and bile acid synthesis, and upregulation of LDL-C receptor activity.[169-171]

At dosages of 200, 400, 800, and 1200 mg/d, ketoconazole reduced LDL-C levels by 10%, 13%, 33%, and 41% and reduced total cholesterol levels by 7%, 10%, 19%, and 27%, respectively, without affecting high-density lipoprotein or very-low-density-lipoprotein levels but with concomitant hypertriglyceridemia.[78,168,172] Cholesterol reduction occurs rapidly (within 1 month) but is transient because cholesterol levels increase toward pretreatment levels despite ketoconazole continuation.[168] Conversely, hypercholesterolemia and hypertriglyceridemia have been reported after treatment with itraconazole and voriconazole, but the underlying mechanism remains unclear.[163,173]

INVOLVEMENT AND DYSFUNCTION OF THE MALE REPRODUCTIVE SYSTEM

Mycoses

Fungal epididymoorchitis can occur as an isolated entity or, more often, during disseminated infection.[174] Blastomycosis is the predominant mycosis involving the male reproductive organs in up to 10% of cases, although other fungal infections have been reported[45-49,91,95,174-178] (Table 2).

Fungal epididymoorchitis may be asymptomatic and discovered postmortem or can cause scrotal swelling and pain, requiring antifungal therapy and surgical resection.[174] As with any gonadal infection, fungal epididymoorchitis can cause infertility because of gonadal destruction and resultant azoospermia.[179] In addition to invading tissue, fungi can contribute to infertility by inducing antisperm effects and secreting mycotoxin. *Candida guilliermondii* and *Candida albicans* are able to inhibit sperm viability and motility in vitro.[180-182] In fact, a proportion of infertile men and women have antibodies positive for *C guilliermondii*.[180,181] The meaning of this finding is unknown, but restoration of fertility was achieved in some patients after eradication of *C guilliermondii* by ketoconazole.[180,181] *Cryptococcus neoformans* can also cause hypospermia and teratospermia.[183] The *Fusarium* toxin zearalenone and its metabolite zearalenol bind as agonists to estrogen receptor-α and -β, causing hyperestrogenism-mediated decreases in testosterone and libido, azoospermia, and feminization in mammals.[184] Whether such hyperestrogenic effects occur in patients with fusariosis is unclear.

Antifungal Agents

Ketoconazole inhibits testosterone production by Leydig cells in vitro and impairs fertility in animals.[185] The most sensitive site of ketoconazole action in male gonads is 17,20-lyase, which is involved in sex-hormone production (Figure)[134,136,186]; a single 200-mg dose has been reported to selectively inhibit testosterone without altering cortisol levels.[134,136,186] Testosterone inhibition is reversible and dose-dependent, and an inverse relationship exists between serum ketoconazole and testosterone concentrations.[134,136,137,186] Administration of 200 to 600 mg of ketoconazole lowers testosterone levels within 2 to 4 hours, but they recover within 24 hours.[137,186] A lower nadir and longer duration of suppressed testosterone levels occur with increasing ketoconazole doses; in a substantial portion of patients, testosterone suppression was sustained throughout the day with 800 mg of ketoconazole.[137,186]

These antiandrogenic properties account for hypogonadism during high-dose ketoconazole treatment.[186] In patients receiving more than 800 mg/d, oligospermia and azoospermia have been reported in 66% and 22% of patients, respectively.[12,134,172] Decreased libido and impotence developed in 2% to 4% of patients at 400 mg/d and in 12% to 14% at 800 to 1200 mg/d.[12,134,172] Finally, reversible gynecomastia appeared after as little as 1 month or after as many as 32 months of ketoconazole treatment in 2% to 7%, 14%, 23%, and 33% of patients treated with 400, 800, 1200, and 2000 mg/d, respectively.[12,134,172] Ketoconazole-mediated in-

creases in the estradiol:testosterone ratio appear to be fundamental to the pathogenesis of gynecomastia.[187]

Ketoconazole's antiandrogenic properties have clinical applications. For instance, Glass[188] advocated ketoconazole for testing gonadotropin reserve in infertile men. Because of its rapid onset of action and ability to block both adrenal and gonadal androgen synthesis, ketoconazole is used for advanced prostate cancer.[189] Administration of 400 mg every 8 hours causes initial testosterone lowering to castration levels.[134,189] Despite subsequent testosterone-level increases driven by compensatory increases in LH levels, many patients with prostate cancer have striking biochemical and clinical responses, leading to tumor regression and symptom improvement. To prevent compensatory increases in LH levels and diurnal testosterone fluctuations observed with ketoconazole monotherapy, a gonadotropin-releasing hormone analogue such as leuprolide is often coadministered.[134,189]

Ketoconazole has also been used for treatment of autonomous Leydig cell hyperactivity in children with precocious puberty, resulting in remarkable behavioral and clinical improvement with decreased growth and skeletal maturation rates.[190] Topical ketoconazole has been suggested as an adjunct to finasteride for androgenetic alopecia.[191] By inhibiting 5α-reductase and competitive binding to androgen receptors,[192,193] ketoconazole may prevent dihydrotestosterone attachment to androgen receptors in hair follicles, a key step in alopecia development.

At extremely high doses, fluconazole has caused mild testosterone inhibition in vitro, exhibiting less than 1% of ketoconazole's potency and causing reversible oligospermia and sperm dysmotility in rabbits.[194] However, administration at 50 mg/d does not lower basal or gonadotropin-stimulated testosterone levels, and no antiandrogenic complications have been observed in patients treated at even higher doses.[195] Similarly, at 200 to 400 mg/d, itraconazole does not affect testosterone production, and decreased libido, impotence, and gynecomastia are sporadically reported in less than 1% of treated patients.[151,173] In animals, AMB and nystatin cause oligospermia and sperm dysmotility, but their effects on human fertility remain unknown.[196]

INVOLVEMENT AND DYSFUNCTION OF THE FEMALE REPRODUCTIVE SYSTEM

Mycoses

Several mycoses can infiltrate the uterus, salpinx, and ovaries during dissemination[45,93,95,174,197-203] (Table 2). Conversely, isolated genital blastomycosis and histoplasmosis can be acquired by sexual transmission.[199,202] Fungal infections of female reproductive organs can be asymptomatic or present as endometritis and/or tubo-ovarian abscess, causing menstrual irregularities, menorrhagia, dysmenorrhea, anovulation, and/or infertility.[197-203]

Mycoses can cause dysregulation of the reproductive endocrine axis via mechanisms other than tissue invasion. For example, Arora et al[204] reported hyperprolactinemia-induced amenorrhea and galactorrhea in a woman with blastomycosis involving the pleural cavity. This was attributed to prolactin production by the chest-wall inflammatory process, a well-described condition that causes prolactin release. Furthermore, the *Fusarium* toxin zearalenone can induce hyperestrogenism in female mammals but rarely in humans, leading to decreased LH and progesterone levels, infertility, vulvovaginitis, and decreased milk production.[184]

Antifungal Agents

Ketoconazole inhibits ovarian aromatase in vitro and in animals, but aromatase blockade in human ovaries is less pronounced than androgen blockade by 17,20-lyase.[205] Consequently, ketoconazole does not cause sustained or predictable estrogen-level lowering in women; a single 200-mg dose caused a 16% decrease in estradiol levels at the luteal phase.[134,205,206] However, such modest decreases are transient, and increases to pretreatment levels occur with continuous treatment. In contrast, women with adrenal tumor–induced estrogen oversecretion have experienced marked, sustained estradiol reductions with high-dose ketoconazole.[142] However, it is unclear whether estrogen reduction resulted from aromatase inhibition or androgen synthesis blockade and therefore estrogen precursor deprivation. Ketoconazole also decreases ovarian progesterone production, impairs early uterine implantation, and decreases decidual response after implantation, suggesting interference with early pregnancy.[207] Ketoconazole-mediated sex-hormone dysregulation has been reported to result in dose-dependent menstrual irregularities in 6% and 19% of women given 400 and 800 mg/d, respectively.[172,208]

Because of its potential to inhibit ovarian aromatase, high-dose ketoconazole has been studied in women with advanced breast cancer resistant to conventional chemotherapy.[59,206] Ketoconazole did not reliably reduce estrogen levels, and only 1 of 14 patients had a partial response after adding ketoconazole to aminoglutethimide.[206] Conversely, because of its ability to substantially block ovarian androgen synthesis, physicians have used ketoconazole for ovarian hyperandrogenism syndromes, including polycystic ovarian syndrome and hyperthecosis, with considerable improvement in acne, hirsutism, and amenorrhea.[209]

Triazoles do not appreciably affect production of sex hormones in women, and menstrual irregularities are rarely reported with fluconazole and itraconazole; however, 6% of patients treated with posaconazole for more than 6 months developed such symptoms.[173,210] Because flucon-

azole inhibits estrogen metabolism and increases ethinyl estradiol levels in women taking oral contraceptives,[211] long-term fluconazole therapy in these women may induce hyperestrogenic effects. Such interaction with oral contraceptive treatment may also occur with voriconazole.[212] Conversely, inadvertent pregnancies have been reported in patients taking oral contraceptives and itraconazole because estrogen metabolism was enhanced by the latter.[213]

CONCLUSION

Fungal infections may have pleiotropic effects on the endocrine system associated with pituitary, thyroid, parathyroid, pancreatic, adrenal, and reproductive organ infiltration and may lead to metabolic and electrolytic disturbances. Similar complications may arise during treatment of such infections with systemic antifungal agents. A better understanding and high index of suspicion for these infections might result in earlier recognition and in amelioration of the morbidity and mortality associated with the complex interaction between fungi and/or their treatment and the endocrine/metabolic system.

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